The Unhealthy Anterior Pituitary

Introduction

Pituitary disorders occur because the pituitary makes either too little or too much of a hormone. The cause of the hormone excess or deficiency may also have effects independent from those of the excess or deficiency—such as a pituitary adenoma compressing the optic chiasm, leading to visual defects—but the pituitary problem will always include deficient or excess hormone. This lesson explores the excess production of prolactin (the most common hormone released from a pituitary adenoma) and the growth hormone axis and excess production of growth hormone and then closes with the causes of panhypopituitarism. We've chosen to group these subjects together because these conditions do not have another endocrine gland in their pathway—prolactin directly stimulates the release of breast milk, ADH affects the collecting duct, and growth hormone's regulation is entirely in the brain (and not at the liver). The other disorders of the anterior pituitary that could result in an excess or deficiency in other endocrine glands will be discussed in the context of those glands later in the Endocrine module.

Overproduction and Underproduction

The **anterior pituitary** is truly an endocrine gland. Its cells have receptors, it listens for signals from the hypothalamus, and it releases hormones into the circulation in response. Therefore, the mechanisms of overproduction and underproduction vary greatly. Excess production of a hormone can be caused by the **unregulated proliferation of the cells of the anterior pituitary** (pituitary adenoma) or by **excess stimulation of the anterior pituitary** (which means hypothalamic excess, which is super rare); the target organ of the anterior pituitary could develop its own ability to make a hormone, even without stimulation from the anterior pituitary (**adenoma**), or the hormone could be made by another tissue that isn't supposed to make it but makes it anyway, such as a **malignancy**. In each case, there would be negative feedback up the axis causing varying degrees of change in precursor hormones.

The underproduction of a hormone can be due to a **loss of tropic signal** from the hypothalamus, **loss of the anterior pituitary**, or loss of the **target gland**. Again, hypothalamic injury is extremely rare, so the absence of a hormone is most likely due to the loss of the anterior pituitary.

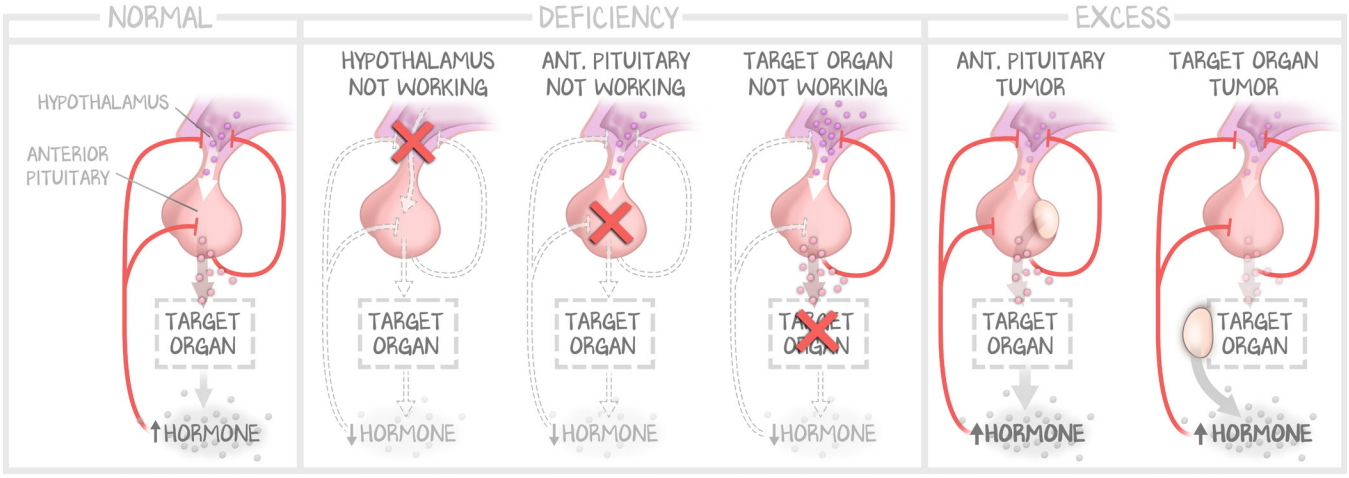

Figure 3.1: Mechanisms of Hormone Excess or Deficiency—Pituitary
A visualization of the preceding two paragraphs. The hypothalamic-pituitary-organ axes feedforward down their axis. A deficiency in the final hormone can be due to a failure of any organ in the axis—hypothalamus, anterior pituitary, or target organ. Excess hormone can be due to excessive activity of any of the three but is almost always due to either excess pituitary (pituitary adenoma) or organ ("organ adenoma") hormones. Not depicted are less common malignancies and hypothalamic excess.

The **posterior pituitary** does not proliferate, nor does it require a receptor to stimulate it. The posterior pituitary is neural tissue, incapable of proliferating, so it cannot become malignant. Thus, excess posterior pituitary hormone must mean that it is coming from somewhere else, which usually means cancer. Likewise, a deficient posterior pituitary hormone implies a loss of neural tissue, such as a stroke or brain trauma.

Pituitary Adenoma in General

A pituitary adenoma represents a **monoclonal proliferation** of **nonmalignant cells** of the anterior pituitary. Unregulated proliferation results in the generation of a mass within the pituitary. That mass is going to be made up of the cell type that acquired the proliferation mutation. If those cells retain the ability to make and release hormone, the adenoma is termed **functioning**. Functioning adenomas present with the symptoms of excess hormone. The most common functioning adenomas are GH-secreting and prolactin-secreting tumors. If the cell the adenoma is derived from is not hormone-secreting, the tumor will not secrete hormone and is termed **nonfunctioning**. If adenomas get large enough, they may cause a mass effect, inducing the **loss of hormone function** in other cells. Because nonfunctioning tumors do not cause symptoms until they are large enough to cause a mass effect, nonfunctioning adenomas tend to be larger at diagnosis. A large mass (> 1 cm) is termed **macroadenoma**, whereas a small mass (< 1 cm) is termed **microadenoma**. Up to 15% of autopsies find a clinically silent, nonfunctioning, and asymptomatic microadenoma, termed "incidentaloma."

In prolactinomas and GH-secreting adenomas (which constitute the majority of pituitary adenomas), there have been some consistent gene mutations that suggest a molecular cause for their unregulated proliferation. In adenomas, there is often a gain-of-function mutation that results in proliferation and hormone secretion. Those that are most frequently identified in pituitary adenomas are **G-protein mutations**. A number of mutations can lead to adenomas. The one seen in the majority of pituitary adenomas is a mutation of the gene ***GNAS*** (guanine nucleotide-binding protein, α-subunit). *GNAS* codes for the α-subunit (G_s) of the GPCR. Mutations in *GNAS* that lead to adenoma result in the normally transient G_s subunit becoming constitutively active, meaning that the activation of the receptor by a tropic signal is not required for the G-protein to have a stimulatory effect.

The typical pituitary adenoma is soft and well circumscribed. Small adenomas may be confined to the sella turcica, but with expansion, they frequently erode the sella turcica. Larger lesions usually extend superiorly through the sella diaphragm and into the suprasellar region, where they often compress the optic chiasm and adjacent structures, such as some of the cranial nerves. Compression of the optic chiasm provokes **bitemporal hemianopsia**, the loss of peripheral vision.

Diagnosing a pituitary adenoma relies on identifying the syndrome of hormone excess, performing the screening test, ruling out other causes of the symptoms, and then confirming with an **MRI of the brain**. Surgical resection of the adenoma is the treatment of choice for all except prolactinoma.

Prolactinoma

Prolactinomas are the most common functioning pituitary adenomas. They release prolactin. **Prolactinemia**, an elevation of the prolactin level in the blood, causes **amenorrhea and galactorrhea** in women (who tend to notice their menses stopping and their breasts leaking milk) but has few overt effects in men (decreased libido). Thus, women tend to present with microadenomas, whereas men present with macroadenomas. Prolactinemia may be the result of other pathologies than simply an adenoma—prolactinemia does not necessitate prolactinoma. Prolactin is inhibited by the hypothalamus through the release of dopamine. The loss of that inhibitory signal results in prolactin expression. Hypothalamic strokes are rare, so there is often something else. **Dopamine antagonists** (treatment for schizophrenia, metoclopramide) can cause amenorrhea and galactorrhea by stimulating the dopamine

receptor. Surprisingly, **in higher-than-normal concentrations, TRH** can stimulate prolactin release—not by interfering with the inhibitory dopamine signal, but by acting on some other (poorly understood) receptor and doing what TRH does to thyrotropes—G_q-IP_3-Ca^{2+}-PKC. Therefore, severe hypothyroidism, diagnosed by an **elevated TSH** level, can cause prolactinemia. Finally, **pregnancy** induces prolactinemia.

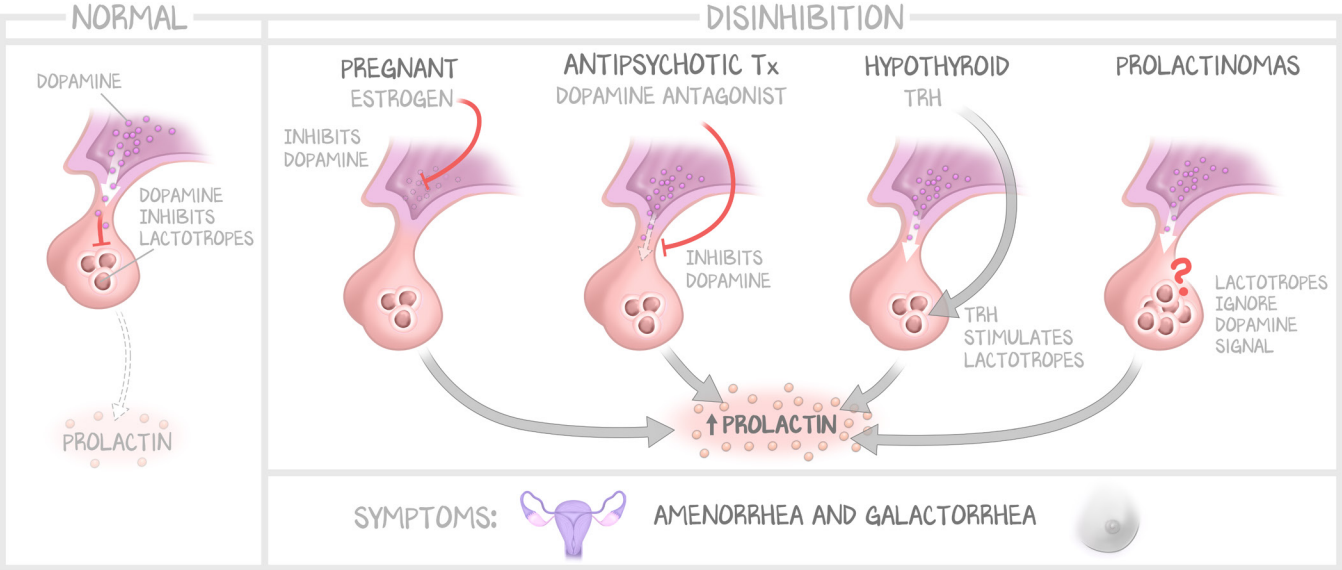

Figure 3.2: Prolactinemia
Excess prolactin causes amenorrhea and galactorrhea in women. The lactotropes' inherent tendency is to make prolactin, and they are under constant inhibition via hypothalamic dopamine. Prolactinemia is, therefore, due to the disinhibition of lactotropes. Pregnancy does this naturally by inhibiting the release of dopamine from the hypothalamus. Antipsychotics do this artificially by blocking dopamine receptors. Hypothyroidism, via excess TRH release, can stimulate lactotropes. Finally, prolactinomas proliferate and produce prolactin despite the dopamine signal.

Once other conditions have been ruled out (pregnancy test, TSH, and medication screen), measuring **prolactin levels** confirms the prolactinemia as the cause of the symptoms. Once confirmed, an MRI of the brain will reveal the mass. **Medical therapy is preferred** for prolactinomas. Patients are treated with dopamine agonists, enhancing the inhibitory effect of the dopamine receptor on lactotropes. **Cabergoline**, a newer dopamine agonist, is preferred over the older bromocriptine. Those that grow or fail to regress on medical treatment are excised and also often irradiated.

Prolactinomas often do not bear the *GNAS* mutation. This makes sense because there is an inhibitory signal from the hypothalamus rather than a stimulatory one, and *GNAS* is in a second messenger cascade that results in stimulation of the cell. Sporadic prolactinomas often bear a mutation in **PIT-1**, a nuclear transcription factor normally expressed in the growth hormone pathway.

Growth Hormone Details

In the last lesson, we learned the growth hormone (GH) axis. The hypothalamus produces growth hormone-releasing hormone (GHRH, stimulates GH release) and somatostatin (inhibits GH release). GH's effector organ is the **liver**, which makes **insulinlike growth factor-1 (IGF-1)**. IGF-1 induces anabolic effects similar to those of insulin but does not modify blood glucose. GH inhibits its own production in a short feedback loop—GH inhibits more GH secretion. But the more potent signal is IGF-1; IGF-1 **indirectly inhibits** the release of GH by **stimulating somatostatin** release from the paraventricular nucleus of the hypothalamus and **inhibiting GHRH** release from the arcuate nucleus of the hypothalamus. IGF-1 **directly inhibits** the release of GH at the level of the pituitary as expected.

The release of GH by somatotropes is regulated by three hormones—somatostatin, GHRH, and ghrelin. All three are peptide hormones, and receptor activation results in GTP-related protein activity. **GHRH** binds to its receptor, a G protein-coupled receptor that activates (stimulates) the G_s-AC-cAMP-PKA pathway. The end result of the pathway is the influx of calcium. Calcium influx results in the fusion of the vesicles and exocytosis of GH, very similar to what you saw in synapses (General Physiology #8: *Synapses*). **Somatostatin** binds to its receptor and activates (inhibits) the G_i-AC-cAMP-PKA pathway. **Ghrelin** is released from the stomach cells in response to fasting. The theory is that if the stomach is empty, then it just finished digesting a meal. When the stomach is done with it, pancreatic enzymes and gallbladder bile will finish the digestion of the food bolus, and the intestines will absorb the monomers (Gastrointestinal: Digestion and Absorption #8: *Physiology of Digestion and Absorption*). Ghrelin is the signal to the anterior pituitary that there will be resources for growth. Thus, ghrelin activates the GH axis. It does this by stimulating G_s by activating its own receptor—the same intracellular second messenger, a different receptor. **GH release is episodic**, with a near hundred-fold increase in GH levels during bursts. Bursts occur mostly while asleep, confirming what championship bodybuilders have said for decades—sleep is required to grow muscle. The GH receptor, a **receptor tyrosine kinase**, acts through the JAK/STAT second messenger system.

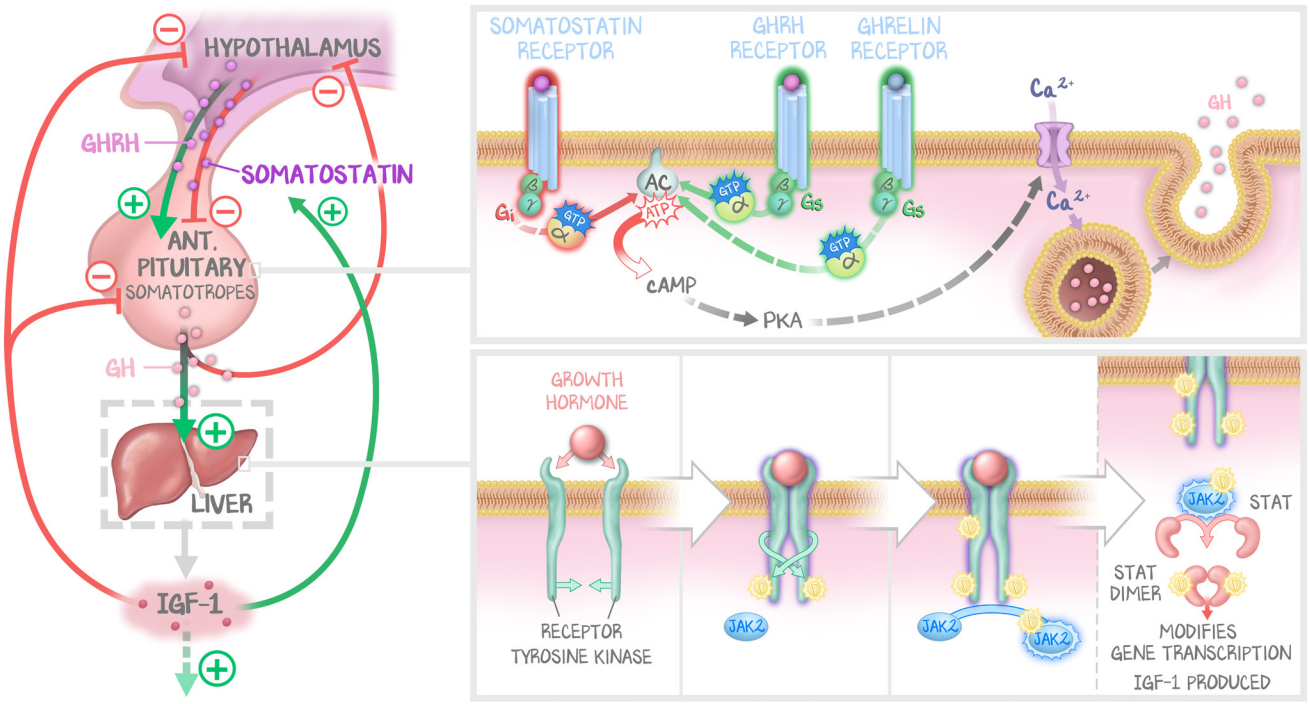

Figure 3.3: Growth Hormone Axis Regulation
From the hypothalamus, both GHRH and somatostatin are released. GH release from somatotropes is initiated by the opening of calcium channels and the fusion of GH-containing vesicles with the plasma membrane. Calcium influx, and therefore vesicular fusion, is stimulated by G_s-AC-cAMP-PKA. Therefore, GH release is stimulated by GHRH binding to its receptor (G_s) and inhibited by somatostatin binding to its receptor (G_i). On hepatocytes, the GH receptor is a receptor tyrosine kinase that utilizes the JAK/STAT pathway. The result is the synthesis and release of IGF-1. IGF-1 inhibits GH release from the anterior pituitary while stimulating somatostatin release from the hypothalamus and inhibiting GHRH release from the hypothalamus.

Growth hormone doesn't actually induce growth at all. The direct effects of GH are very similar to those of cortisol. GH is one of the counter-regulatory hormones, those that oppose insulin's actions. Insulin causes glucose uptake by myocytes and adipocytes, fatty acid synthesis and glycogenesis in hepatocytes, triglyceride synthesis (storage of fatty acids) in adipocytes, and protein anabolism in myocytes. Therefore, GH's direct effects are said to be **diabetogenic**—inducing lipolysis in adipose, protein catabolism in skeletal muscle, and gluconeogenesis/glycogenolysis/fatty acid oxidation in hepatocytes. GH excess, therefore, presents with insulin resistance and hyperglycemia.

So why is it named *growth* hormone? The direct, short-term effect of GH on the cells of metabolism is to mobilize energy. GH causes indirect, long-term growth through the release of IGF-1. GH may be pulsatile and vary greatly throughout the day, but IGF-1 does not vary. **Growth correlates with plasma concentrations of IGF-1,** not GH. The growth spurt during puberty is tightly correlated with the levels of IGF-1. IGF-1 also acts through its own receptor tyrosine kinase, which coincidentally uses the JAK/STAT second messenger. This **steady level of IGF-1** is why disorders involving GH are diagnosed using IGF-1 levels. And this is not surprising. Because insulin is the most intensely anabolic hormone there is, an insulinlike hormone inducing anabolism is a natural conclusion. IGF-1 does all the things that insulin does—amino acid anabolism, fatty acid synthesis—except increase GLUT4 channels in skeletal muscle and adipose. IGF-1 does NOT cause hypoglycemia.

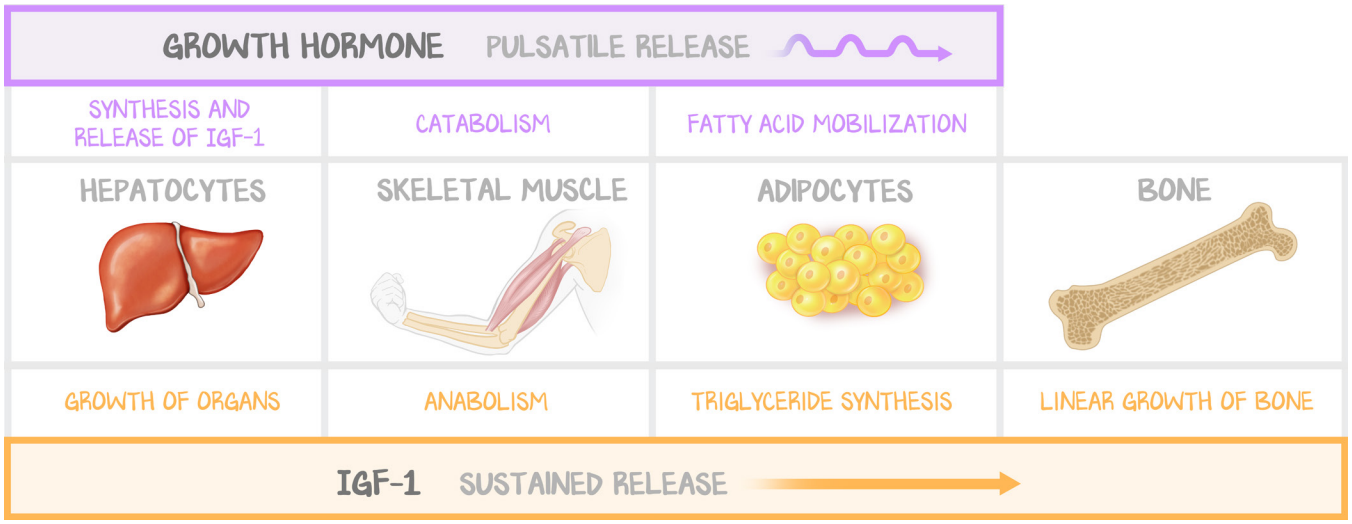

Figure 3.4: Growth Hormone Effects
GH release affects the cells of metabolism to mobilize energy stores using the GH receptor, acting through a receptor tyrosine kinase—fatty acids are mobilized, skeletal muscle is consumed. GH release also induces the liver to release IGF-1. IGF-1 levels are sustained, whereas GH levels are pulsatile. IGF-1 causes the opposite response in the cells of metabolism—fatty acids are stored as triglycerides, and proteins are synthesized in skeletal muscle. In cells not of metabolism, IGF-1 induces growth—long bones grow longer, and any organ that can grow grows bigger. When the system functions appropriately, GH does result in growth, but only through its downstream effector hormone, IGF-1.

Growth Hormone Problems

GH is a diabetogenic hormone, acutely inducing lipolysis in adipose, gluconeogenesis in the liver, and carbohydrate restriction in skeletal muscle. We are going to use that fact to assess GH activity. GH's pulsatile nature means it cannot be assessed in the blood in a meaningful way. And although the variability of GH is too great for it to be useful in testing, its effector molecule, **insulinlike growth factor-1,** remains fairly constant. Excess GH will result in excess IGF-1, whereas deficient GH or GH receptor will result in decreased IGF-1.

IGF-1 is responsible for **linear growth**, a phrase that means "grow in all directions," and an **increase in muscle mass**. Patients who are **deficient in IGF-1** will have **dwarfism**, with a presentation of **short stature**. This short stature differs from that of achondroplasia, another genetic condition that results in short stature, in that achondroplasia does not affect flat bones. In achondroplasia, there is short stature and a normal-sized head. In dwarfism due to IGF-1 deficiency, there is short stature and a small head. This form of dwarfism may result from the inability to produce GH, or, as in **Laron syndrome**, a defective **GH receptor**.

Those patients with **excess IGF-1** will **grow**. IGF-1 induces the **long bones to grow** while they can grow. Because the growth plates fuse during puberty, excessive IGF-1 cannot affect the long bones after they fuse. If a person has excess IGF-1 before puberty ends, they will present with **gigantism**. IGF-1 has a profound effect on the long bones, but IGF-1 makes anything that can grow, grow. Therefore, patients with gigantism also have large flat bones—big hands, big feet, and a big head in addition to the extra height. In patients who develop excess IGF-1 when they are older, long after the fusion of the growth plate, the tissues that can grow will grow. The **skull enlarges**, evidenced by teeth that separate over time. The **fingers enlarge**, evidenced by rings that don't fit anymore. Worse, the **internal organs enlarge,** and patients present with diastolic heart failure, hypertension, diabetes, etc. This presentation is called **acromegaly**.

When considering excess IGF-1, the most likely cause is a **pituitary adenoma**, a benign GH-secreting tumor in the anterior pituitary. The screening tool is to assess IGF-1, which will be elevated. The next test uses the diabetogenic changes from the GH release. GH, if it were following normal regulation, **should decrease with an oral glucose load**. A glucose suppression test that **fails to suppress** GH levels is indicative of an adenoma. An **MRI** will confirm. Unlike in prolactinoma, for which medical treatment is preferred, **surgical resection** is preferred for GH adenomas. Those who do not achieve remission should be treated with medical therapy. Because somatostatin inhibits GH release, artificial somatostatin can be given to limit GH release. Artificial somatostatin is called **octreotide**. In addition, **pegvisomant**, a GH receptor antagonist, can be used to stifle the activity of whatever GH is secreted.

The normal development of puberty is to respond to GH and IGF-1, hit growth spurts, and get tall. Some kids want to be taller than they are. Some kids take longer to reach puberty than others. Most of the time, short stature is **genetic**—if the teenager's parents are short, chances are, the kid is going to be short. When it's not genetics, the next most common cause of short stature in a teenager is a **constitutional growth delay**. That means they are just taking longer than other kids, and they too will get tall if nothing is done. But if there is a defect in the GH pathway and nothing is done for it, puberty progresses without the growth, and when the growth plates fuse, the child will have missed the opportunity to benefit from intervention. Don't give GH to kids who are supposed to be short. Don't give GH to kids who just need a little bit of time to hit their growth spurt. But when a child presents with short stature that is **disproportionate for age and family height history**, evaluation of the **bone age** compared to the child's age will dictate what to do. If the bone age **matches** actual age, and the child is small, this means the bones have been responding to GH, but there just isn't enough signal. These kids need to be intervened on and given **growth hormone supplementation**. If the bone age is younger than actual age, the child merely needs to wait, and they will grow in time.

Panhypopituitarism

Pan-hypo-pituitarism is the lack (-hypo-) of all (pan-) pituitary hormones (-pituitarism). This process can be acute (and obvious) or chronic (and insidious). The pituitary preferentially sustains the hormones needed to keep the host organism alive and sacrifices less necessary functions. For example, reproduction and bulking up are less important than keeping cells active (thyroid hormone) and blood vessels working (cortisol). Loss of **ACTH** means the loss of cortisol, which presents with **hypotension, coma, and death.** Loss of **TSH** means the loss of T_4, which presents with **lethargy, coma, and death**. The loss of FSH, LH, or GH may impact menses or libido but does not present with coma and death. Thus, if there is an insidious process, symptoms may not be overt, and the cause less obvious. If there is an acute process, symptoms are overt, and the cause usually more obvious. **Aldosterone** is under the influence of renin-angiotensin signaling from the kidney, and so is unaffected by panhypopituitarism.

Chronic. Common causes of slowly deteriorating pituitary function are a **tumor** (a nonfunctioning adenoma compressing the good pituitary), **infiltrative diseases** (such as sarcoidosis), and **autoimmune destruction**. Because these processes occur slowly, the pituitary has a chance to adjust. Because LH, FSH, and GH are not necessary for survival, they are cut off first. We can use that fact and the fact that GH is diabetogenic to screen for a GH deficiency. Administration of insulin or **vasopressin** should cause the GH level to rise. A **failure to rise** is indicative of defective GH production.

Acute. Without time to accommodate for the deficiency of life-saving hormones, the patient presents far sicker than in the chronic condition. The "four I's" can help you recall the common causes of acute panhypopituitarism: **Iatrogenic** (surgery, radiation), **Infection, Infarction,** and **Hemorrhage**.

Two specific situations are worth committing to memory—Sheehan's and apoplexy. In **apoplexy**, hemorrhage into the pituitary compromises its function. This usually presents in someone who has already had an adenoma. In **Sheehan's syndrome**, also known as postpartum panhypopituitarism, there is an infarction of the pituitary after experiencing significant blood loss during delivery. Although we cover lactation in detail in the Reproduction module, a brief description is worth mentioning here. Estrogen is a steroid hormone that induces the transcription of prolactin in the anterior pituitary. This increased production is required to prepare the mother's breasts to produce milk and disable the FSH/LH signal for ovulation. A byproduct is that the pituitary hypertrophies as more lactotropes make more prolactin. The size of the pituitary increases, but the vascular supply doesn't, leaving mom's pituitary vulnerable to infarction. If she bleeds a lot during vaginal delivery (hemorrhagic shock) or experiences hypotension from any cause (such as anesthesia), the impaired vascular supply leads to infarction. The most vulnerable cell types are the ones that have been stimulated the most—the lactotropes, so mild hypotension resulting in mild infarction may present with **the inability to lactate** as the first sign. More severe hypotension resulting in more severe infarction will present with more severe disease.

Panhypopituitarism offers us the opportunity to discuss a fundamental feature of endocrinology. Because the hormones travel in the blood, a **deficiency of hormone** can be **treated by supplementing that hormone**. The hypotension caused by a deficiency in cortisol can be treated with the administration of glucocorticoids. The coma and lethargy from deficient thyroid hormone can be treated by giving the patient levothyroxine.